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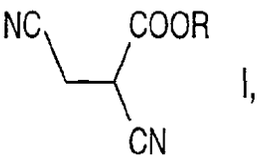
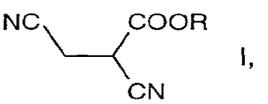
(54) Process for the preparation of 2,3-dicyanopropionates

(57) The invention relates to a process for the preparation of a compound of formula



I,

wherein R represents branched or unbranched $(C_1\text{-}C_6\text{-alkoxy})_{1\text{-}10}\text{-}C_2\text{-}C_6$-alkyl, $C_3\text{-}C_8$-cycloalkyl, allyl, propargyl, phenyl or phenyl-$C_1\text{-}C_6$-alkyl; or a salt thereof; which comprises the reaction of a cyanoacetate of formula



I,

wherein R is defined as in formula I, with formaldehyde or a source thereof in the presence of a cyanide salt. The compounds of formula I are useful as intermediates in the synthesis of pesticidally active compounds.

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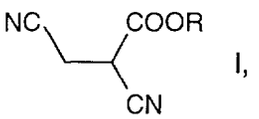
Description

[0001] This invention relates to a process for preparing certain 2,3-dicyanopropionic esters and their use in the synthesis of pesticides and pesticide intermediates.

[0002] Ethyl 2,3-dicyanopropionate was first synthesized by Higson and Thorpe in 1906 (J. Chem. Soc. 89, 1460 (1906)) and later by Dickinson (J. Am. Chem. Soc. 82, 6132 (1960)) by reaction of formaldehyde cyanohydrin with the sodium salt of ethyl cyanoacetate. Due to the inherent problem of having to isolate the highly watersoluble and fairly unstable intermediate formaldehyde cyanohydrin, Hawkins et al. (WO 97/32843, 12.9.97) suggested a process avoiding the cyanohydrin altogether by reacting an alkyl cyanoacetate in the presence of sodium cyanide with formaldehyde. This procedure gives the corresponding 2,3-dicyanopropionic alkyesters in good yields; however, it requires absolutely waterfree conditions. Thus, none of these attempts is totally satisfactory.

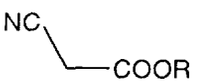
[0003] The present invention, in a first aspect, provides a process for the preparation of 2,3-dicyanopropionic esters which avoids the use of formaldehyde cyanohydrin, simplifies waterfree conditions and gives the required product in high yield and with high purity.

[0004] Therefore, the present invention provides a process for the preparation of a compound of formula



I,

wherein R represents branched or unbranched (C_1-C_6-alkoxy)$_{1-10}$-C_2-C_6-alkyl, C_3-C_8-cycloalkyl, allyl, propargyl, phenyl or phenyl-C_1-C_6-alkyl; or a salt thereof;
which comprises the reaction of a cyanoacetate of formula



II,

wherein R is defined as in formula I, with formaldehyde or a source thereof in the presence of a cyanide salt.

[0005] Preferably, R represents unbranched (C_1-C_2-alkoxy)$_{1-2}$-C_2-C_4-alkyl, C_4-C_6-cycloalkyl or phenyl-C_1-C_2-alkyl, more preferably unbranched C_1-C_2-alkoxy-C_2-C_4-alkyl or phenyl-C_1-alkyl, most preferably unbranched C_1-alkoxy-C_2-C_4-alkyl.

[0006] Suitable salts of cyanides encompass metal salts and organic salts such as tetraalkylammonium, preferably tetrabutylammonium, cyanides. Suitable metal salts are alkali or alkaline earth metal cyanide salts, particularly alkali metal cyanides, especially potassium or sodium cyanide.

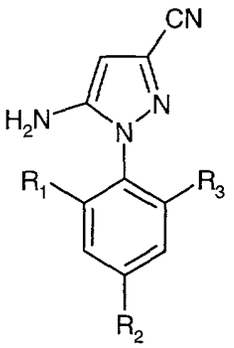
[0007] The product may be isolated as the alkali or alkaline earth metal salt. Preferably, the reaction mixture is acidified, for example with a mineral acid such as sulfuric of hydrochloric acid, to yield the compound of fomula I in the free form.

[0008] The reaction may be carried out with formaldehyde itself; however, it is usually preferred to use the polymerised form known as the commercially available paraformaldehyde.

[0009] The reaction partners can be reacted with one another as they are, i.e. without the addition of a solvent or diluent, e.g. in the melt. In most cases, however, the addition of an inert solvent or diluent, or a mixture thereof, is of advantage. Examples of such solvents or diluents are: aromatic, aliphatic and alicyclic hydrocarbons and halogenated hydrocarbons, such as benzene, toluene, xylene, mesitylene, tetraline, chlorobenzene, dichlorobenzene, bromobenzene, petroleum ether, hexane, cyclohexane, dichloromethane, trichloromethane, tetrachloromethane, dichloroethane, trichloroethene or tetrachloroethene; alcohols, such as methanol, ethanol, propanol, isopropanol, butanol, ethylene glycol, polyethylene glycol, ethylene glycol monomethyl ether, or glycerol; ethers, such as diethyl ether, dipropyl ether, diisopropyl ether, dibutyl ether, tert-butyl methyl ether, ethylene glycol monomethyl ether, ethylene glycol monoethyl ether, ethylene glycol dimethylether, dimethoxydiethylether, tetrahydrofuran or dioxane; ketones such as acetone, methyl ethyl ketone or methyl isobutyl ketone; amides such as N,N-dimethylformamide, N,N-diethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone or hexamethylphosphoric acid triamide; nitriles such as acetonitrile or propionitrile; and sulphoxides, such as dimethyl sulphoxide. Preferably, the reaction is carried out in an alcohol or ether, more preferably in an alcohol. Especially preferred solvents is ethylene glycol monomethyl ether.

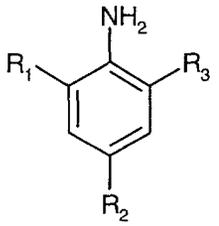
[0010] In a preferred process, a molar equivalent of a compound of formula II is mixed with about a molar equivalent of a cyanide salt and the mixture gradually treated with about a molar equivalent of formaldehyde in its paraformaldehyde precursor form in ethylene glycol monomethyl ether under unhydrous conditions at temperatures of about 0 to about 160°C or at the reflux temperature of the solvent, particularly at temperatures of about 0 to 40°C.

[0011] In a second aspect, the present invention provides a process for the generation of the compound of formula



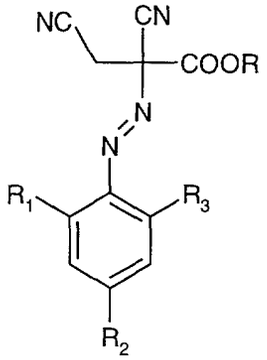
III,

wherein R_1, R_2 and R_3 represent independently of each other halogen, C_1-C_4-haloalkyl, C_1-C_4-haloalkoxy or SF_5; preferably R_1 and R_3 halogen and R_2 trifluoromethyl, trifluoromethoxy or SF_5; which process comprises reacting the compound of formula I with the diazonium salt of a compound of formula



IV,

wherein R_1, R_2 and R_3 are defined as in formula III, to give a compound of formula



V,

wherein R_1, R_2 and R_3 are defined as in formula III; and cyclisation of the compound of formula V by means of a base, preferably ammonia.

[0012] In this process, the reaction partners can be reacted with one another as they are, i.e. without the addition of a solvent or diluent, e.g. in the melt. In most cases, however, the addition of an inert solvent or diluent, or a mixture thereof, is of advantage. Examples of such solvents or diluents are given above. Preferably, the complete reaction sequence is carried out in an alcohol or ether, more preferably in an alcohol. Especially preferred solvents is ethylene glycol monomethyl ether.

[0013] In a preferred process, the diazonium salt of a compound of formula IV may be prepared using common diazotising agents known in the literature, preferably with a molar equivalent of sodium nitrite and a mineral acid such as hydrochloric or sulfuric acid at a temperature of about -10 to about 40°C, particularly from about 0 to about 10°C. Preferably, the diazonium salt is generated in situ in order to ensure its quick reaction with the compound of formula I before being reduced by the alcoholic solution. Subsequent hydrolysis of the ester group and cyclisation is preferably carried out with an aqueous base, particularly aqueous ammonia.

[0014] In a third aspect, the present invention provides a process for the in situ generation of the compound of formula I and the subsequent preparation of the compound of formula III, wherein R_1, R_2 and R_3 represent independently of each other halogen, C_1-C_4-haloalkyl, C_1-C_4-haloalkoxy or SF_5; preferably R_1 and R_3 halogen and R_2 trifluoromethyl, trifluoromethoxy or SF_5; which process comprises

a) reacting a cyanoacetate of formula II with a cyanide salt and formaldehyde or a source thereof, to give a compound of formula I;

b) reacting the compound of formula I thus obtained with the diazonium salt of a compound of formula IV, wherein R_1, R_2 and R_3 are defined as in formula III, to give a compound of formula V, wherein R_1, R_2 and R_3 are defined as in formula III; and

c) cyclisation of the compound of formula V by means of a base, preferably ammonia.

[0015] In this process, the reaction partners can be reacted with one another as they are, i.e. without the addition of a solvent or diluent, e.g. in the melt. In most cases, however, the addition of an inert solvent or diluent, or a mixture thereof, is of advantage. Examples of such solvents or diluents are given above. Preferably, the complete reaction sequence is carried out in an alcohol or ether, more preferably in an alcohol. Especially preferred solvents is ethylene glycol monomethyl ether.

[0016] In a preferred process, reaction step a) is carried out as described above, whereby the product of step a) is generally acidified with an alcoholic solution of a mineral acid. The diazonium salt of a compound of formula IV required in step b) may be prepared using common diazotising agents known in the literature, preferably with a molar equivalent of sodium nitrite and a mineral acid such as hydrochloric or sulfuric acid at a temperature of about -10 to about 40°C, particularly from about 0 to about 10°C. Preferably, the diazonium salt is generated in situ in order to ensure its quick reaction with the compound of formula I before being reduced by the alcoholic solution. Subsequent hydrolysis

of the ester group and cyclisation in step c) is preferably carried out with an aqueous base, particularly aqueous ammonia.

[0017] The compound of formula III is an important intermediate for the preparation of pesticidally active compounds.

[0018] The following non-limiting examples illustrate the present invention.

Example 1: 2-Methoxyethyl 2,3-dicyanopropionate

[0019] 2-Methoxyethylcyanoacetate (3.5 ml) and sodium cyanide (1.72 g) are suspended in 2-methoxyethanol (18 ml) and treated with paraformaldehyde (1.05 g) in portions under ice-cooling. After addition the mixture is left to warm up to room temperature and stirred for 6 hours. The reddish mixture is then acidified to pH 2 with ca. 4 ml aqueous hydrochloric acid under ice-cooling and finally the solvent evaporated at 55°C in vacuo. The residue is extracted with diethyl ether/water, the water phase is washed with diethyl ether, the combined organic phases are washed twice with water and then with a saturated sodium chloride solution, dried, filtered and evaporated to dryness in vacuo. The residue is distilled at 180°C and 0.08 mbar to give the title compound as brownish oil.

Example 2: 5-amino-3-cyano-1-(2,6-dichloro-4-trifluoromethylphenyl)-pyrazole

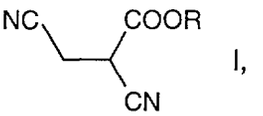
[0020] To 2-Methoxyethylcyanoacetate (491 mg), dissolved in 2-methoxyethanol (4 ml), aqueous hydrochloric acid (0.65 ml) and then 2,6-dichloro-4-trifluoromethylaniline (575 mg), dissolved in 2-methoxyethanol (2 ml), is added under a nitrogen atmosphere. At 5 to 10°C, an aqueous solution (1 ml) of sodium nitrite (242 mg) is added dropwise within 2 minutes and the mixture stirred for 3 hours under ice-cooling. The mixture is then set to pH 9 by addition of aqueous ammonia (25%) and stirred overnight at ambient temperature. After evaporation of the solvent the residue is extracted with ethyl acetate / water, and the organic phase washed twice with water and with a saturated sodium chloride solution, dried, filtered and evaporated to dryness in vacuo. The residue is recrystallized from toluene to give the title compound, m.p. 141-2°C.

Example 3: 5-amino-3-cyano-1-(2,6-dichloro-4-trifluoromethylphenyl)-pyrazole

[0021] 2-Methoxyethylcyanoacetate (2.7 ml) and sodium cyanide (1.33 g) are suspended in 2-methoxyethanol (14 ml) and treated with paraformaldehyde (0.81 g) in portions under ice-cooling. After addition the mixture is left to warm up to room temperature and stirred for 6 hours. The reddish mixture is then acidified to pH 2 with ca. 3 ml aqueous hydrochloric acid under ice-cooling and 2,6-dichloro-4-trifluoromethylaniline (5.75 g), dissolved in 2-methoxyethanol (20 ml), is added within 5 minutes. At 5 to 10°C, an aqueous solution (10 ml) of sodium nitrite (2.42 g) is added dropwise within 2 minutes and the mixture stirred for 3 hours under ice-cooling. The mixture is then set to pH 9 by addition of aqueous ammonia (25%) and stirred overnight at ambient temperature. After evaporation of the solvent the residue is extracted with ethyl acetate / water, and the organic phase washed twice with water and with a saturated sodium chloride solution, dried, filtered and evaporated to dryness in vacuo. The residue is recrystallized from toluene to give the title compound, m.p. 141-2°C.

Claims

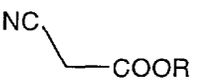
1. A process for the preparation of a compound of formula



I,

wherein R represents branched or unbranched $(C_1\text{-}C_6\text{-alkoxy})_{1\text{-}10}\text{-}C_2\text{-}C_6\text{-alkyl}$, $C_3\text{-}C_8$-cycloalkyl, allyl, propargyl, phenyl or phenyl-$C_1\text{-}C_6$-alkyl; or a salt thereof;

which comprises the reaction of a cyanoacetate of formula

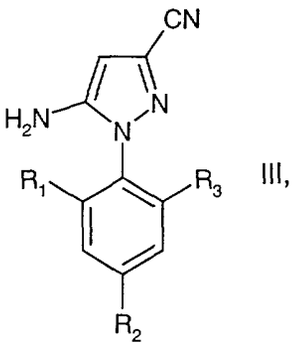


II,

wherein R is defined as in formula I, with formaldehyde or a source thereof in the presence of a cyanide salt.

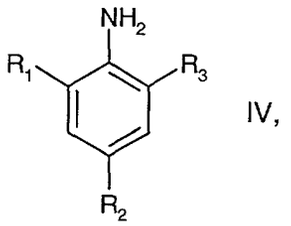
2. A process according to claim 1 wherein the reaction is carried out at temperatures of about 0 to about 160°C or at the reflux temperature of the solvent.

3. A process for the preparation of a compound of formula



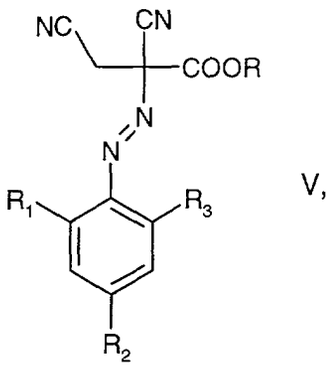
III,

wherein R_1, R_2 and R_3 represent independently of each other halogen, C_1-C_4-haloalkyl, C_1-C_4-haloalkoxy or SF_5; which process comprises reacting the compound of formula I with the diazonium salt of a compound of formula



IV,

wherein R_1, R_2 and R_3 are defined as in formula III, to give a compound of formula



V,

wherein R_1, R_2 and R_3 are defined as in formula III; and cyclisation of the compound of formula V by means of a base.

4. A process for the preparation of a compound of formula III, wherein R_1, R_2 and R_3 represent independently of each other halogen, C_1-C_4-haloalkyl, C_1-C_4-haloalkoxy or SF_5; which process comprises

a) reacting a cyanoacetate of formula II with a cyanide salt and formaldehyde or a source thereof, to give a compound of formula I;
b) reacting the compound of formula I thus obtained with the diazonium salt of a compound of formula IV, wherein R_1, R_2 and R_3 are defined as in formula III, to give a compound of formula V, wherein R_1, R_2 and R_3 are defined as in formula III; and
c) cyclisation of the compound of formula V by means of a base.

5. A process according to any one of the previous claims, wherein R represents unbranched C_1-C_2-alkoxy-C_2-C_4-alkyl or phenyl-C_1-alkyl.

6. A process according to any one of the previous claims, wherein the source of formaldehyde is paraformaldehyde.

7. A process according to any one of the previous claims, wherein the reaction is performed in presence of ethylene glycol monomethyl ether as a solvent.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 01 11 3967

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
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X	AIZENCANG, G. ET AL.: "Synthesis of Isoornithines and Methylputrescines. An Evaluation of Their Inhibitory Effects on Ornithine Decarboxylase" JOURNAL OF MEDICINAL CHEMISTRY, vol. 38, no. 21, 1995, pages 4337-4341, XP001018869 * example 3A *	1,2,5-7	
A	EP 0 295 118 A (MAY & BAKER LTD) 14 December 1988 (1988-12-14) * reference example 7 *	1,2,5-7	
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The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
MUNICH	7 January 2002	Janus, S

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C01)

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Application Number
EP 01 11 3967

CLAIMS INCURRING FEES

The present European patent application comprised at the time of filing more than ten claims.

☐ Only part of the claims have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims and for those claims for which claims fees have been paid, namely claim(s):

☐ No claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims.

LACK OF UNITY OF INVENTION

The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

see sheet B

☒ All further search fees have been paid within the fixed time limit. The present European search report has been drawn up for all claims.

☐ As all searchable claims could be searched without effort justifying an additional fee, the Search Division did not invite payment of any additional fee.

☐ Only part of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the inventions in respect of which search fees have been paid, namely claims:

☐ None of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the invention first mentioned in the claims, namely claims:

European Patent Office

LACK OF UNITY OF INVENTION
SHEET B

Application Number
EP 01 11 3967

The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

1. Claims: 1,2,4 (entirely), 5-7 (in part)

   Process for the preparation of compounds of formula (I), as well as process for their preparation and further processing to prepare the compounds of formula (III)

2. Claims: 3 (entirely), 5-7 (in part)

   Process for the preparation of compounds of formula (III) starting from compounds of formula (I).

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 01 11 3967

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
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07-01-2002

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EPO FORM P0459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 01 11 3967

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